

**REMARKS**

Claims 1-26 are pending in this patent application. Claims 9-19 have been amended. After the amendments have been entered, Claims 1-26 will be pending.

As a preliminary matter, Applicants note that references AE, AG, AR, BT, CE, CG, CN, DI, and DJ were not initialed on the copy of the Form PTO-1449 which was returned with the Office Action. Since the Office Action does not specifically discuss the Form PTO-1449, Applicants suspect that the above references were not initialed because copies of the references were not available to the Examiner. Accordingly, we intend to submit copies of the above references, along with copies of the previously filed Information Disclosure Statement and Form PTO 1449, under separate cover.

Applicants hereby request that the references listed on the Form PTO-1449 be considered by the Examiner and an initialed copy of the Form PTO-1449 be returned to Applicants.

The Office Action appears to object to the application under 37 C.F.R. §1.172(a) as allegedly lacking the written consent of all assignees. However, a properly executed Consent of Assignee for Reissue was filed with the U.S. Patent and Trademark Office on September 29, 1999. The Consent of Assignee was signed by an officer of ISIS Pharmaceuticals, Inc. The Assignments filed in connection with this patent, as well as the Consent of Assignee, establishes ISIS Pharmaceuticals, Inc. as the assignee of the entire interest in the patent for which reissue is sought. For the Examiner's convenience, a copy of the previously filed Consent of Assignee accompanies this response. Accordingly, the Consent of Assignee is believed to be proper and the objection to the specification under 37 C.F.R. §1.172(a) should be withdrawn.

Claim 11 has been amended to correct a typographical error in the spelling of the term "benzoyladenine," as suggested in the Office Action.<sup>1</sup>

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<sup>1</sup> Although the Office Action indicates that the term "benzoyladenine" is misspelled in Claim 10, Claim 10 does not appear to recite the term "benzoyladenine."

The Declaration is alleged to be defective for failing to contain a statement that all errors which are being corrected in the reissue application arose without any deceptive intention on the part of applicant. However, the Declaration filed with the U.S. Patent and Trademark Office on January 28, 2000, is believed to include the requisite statement (see, Declaration filed January 28, 2000 at page 3 (just above the heading "OFFER TO SURRENDER ORIGINAL PATENT 37 C.F.R. §1.178")). Accordingly, the objection to the Declaration should be withdrawn.

The specification stands objected to because the reissue specification was not prepared from cut-up soft copies of the original patent. Although the patent rules allow a reissue application to be prepared from cut-up copies of the original patent, Applicants are not aware of any requirement that the specification be so prepared. However, solely to advance prosecution of the present application, Applicants are providing herewith the reissue specification prepared from a cut-up copy of the original patent.

The specification appears to be objected to because the list of references to be printed at the end of the specification allegedly does not re-cite the references listed at the end of the patent. However, the list of references at the end of the specification is believed to be identical to the list of references cited at the end of the issued patent. Accordingly, the objection to the specification should be withdrawn.

Claims 9-19 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because of the use of the term "general" in the claim preamble. Applicants believe that those skilled in the art would readily understand that the word "general," as it is used to modify the noun "formula" in the claims, is intended to clarify that the recited formulas contain variables and, therefore, are general in nature. However, solely to advance prosecution of the present application, Claims 9-19 have been amended to delete the word "general." Accordingly, the rejection of Claims 9-19 under 35 U.S.C. §112, second paragraph, is believed to be overcome.

Claims 20-26 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Sproat and Gait (*Solid-phase synthesis of oligodeoxyribonucleotides by the phosphotriester method, Oligonucleotide Synthesis: A practical approach*, Chapt. 4), in combination with Sterzycki et al.

(published European Patent Application No. EP 0316017). In making the rejection, the Office Action alleges that it would have been obvious to use the modified fluoronucleosides of Sterzycki et al. in place of those disclosed in Sproat et al. However, the Office Action fails to identify any reason why a person of ordinary skill in the art would have been motivated to make this substitution.

As will be recognized, claims cannot be found obvious in view of prior art references unless the references themselves suggest that their respective teachings should be modified in a way that would produce the claimed invention. *Berghauser v. Dann*, 204 U.S.P.Q. 393 (D.D.C. 1979); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 U.S.P.Q. 929 (Fed. Cir. 1984). There must be something in the prior art that would have motivated persons of ordinary skill to make any necessary modifications. *In re Stencel*, 4 U.S.P.Q.2d 1071, 1073 (Fed. Cir. 1987), *accord*, *Ex parte Marinaccio*, 10 U.S.P.Q.2d 1719 (Pat. Off. Bd. App. 1989). In this respect, the following statement by the Patent Office Board of Appeals is noteworthy:

Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." .....Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would *impel* one skilled in the art to do what the patent applicant has done. *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993) (citations omitted; emphasis added).

Here, the Office Action does not identify any "motivating force" that would have "impelled" persons of ordinary skill to modify the disclosure of the Sproat reference in a manner that would have produced one of Applicants' claimed inventions. Although the Office Action alleges that those of ordinary skill would have been motivated to modify the DNA synthesis procedure disclosed by the Sproat reference by having it employ the nucleosides disclosed by the Sterzycki reference, the "reasons" provided for such motivation are simply not credible. The

Office Action, for example, contends that those of ordinary skill would have been motivated to modify the Sproat synthesis procedure by a desire to construct recombinant DNA. The proposed modification, however, clearly would not have produced DNA, but a significantly different type of molecule including the 2'-fluoro groups and arabino sugars found in the Sterzycki nucleosides.

The Office Action alternatively contends that persons of ordinary skill would have been motivated to modify the Sproat procedure by a desire to effect site directed mutagenesis. Such persons, however, would have recognized that the 2'-fluoro groups and arabino sugars found in compounds produced in accordance with the modification are ill-suited for use in site directed mutagenesis, which requires a naturally-occurring nucleic acid. Since there is no evidence of record suggesting that those of ordinary skill in the art would have been motivated to modify the teachings of the Sproat reference and the Sterzycki reference in the manner proposed in the Office Action, the rejection of claims 20-26 for alleged obviousness is improper and should be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

In view of the foregoing, it is respectfully submitted that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are requested.

Respectfully submitted,



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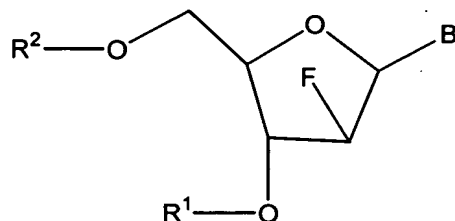
Date: 3/29/2001

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

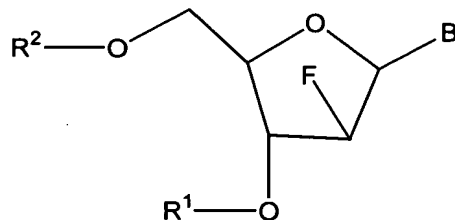
Claims 9-19 have been amended as follows:

9. (Amended) The compound having the [general] formula:



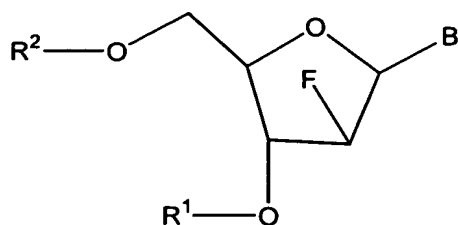
wherein B is N<sup>2</sup>-isobutyrylguanine, R<sup>1</sup> and R<sup>2</sup> are both H.

10. (Amended) The compound having the [general] formula:



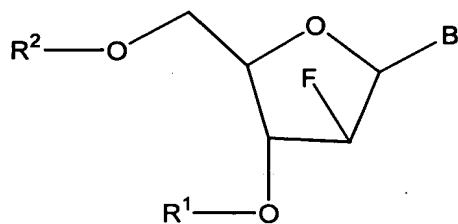
wherein B is N<sup>4</sup>-benzoylcytosine, R<sup>1</sup> and R<sup>2</sup> are both H.

11. (Amended) The compound having the [general] formula:



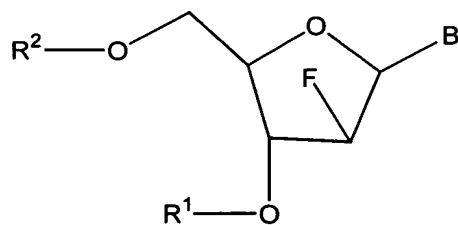
wherein B is [N<sup>6</sup>-benzoyladeneine] N<sup>6</sup>-benzoyladenine, R<sup>1</sup> and R<sup>2</sup> are both H.

12. (Amended) The compound having the [general] formula:



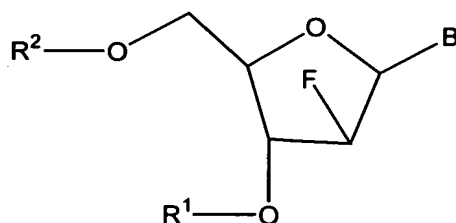
wherein B is N<sup>2</sup>-isobutyrylguanine, R<sup>1</sup> is H and R<sup>2</sup> is 4,4'-dimethoxytrityl.

13. (Amended) The compound having the [general] formula:



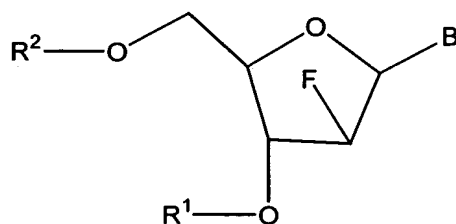
wherein B is N<sup>4</sup>-benzoylcytosine, R<sup>1</sup> is H and R<sup>2</sup> is 4,4'-dimethoxytrityl.

14. (Amended) The compound having the [general] formula:



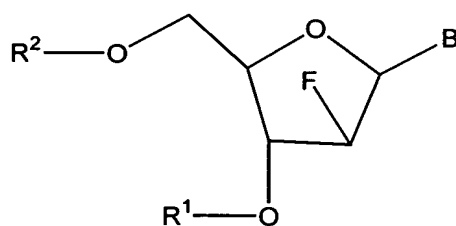
wherein B is N<sup>6</sup>-benzoyladenine, R<sup>1</sup> is H and R<sup>2</sup> is 4,4'-dimethoxytrityl.

15. (Amended) The compound having the [general] formula:



wherein B is thymine, R<sup>1</sup> is H and R<sup>2</sup> is 4,4'-dimethoxytrityl.

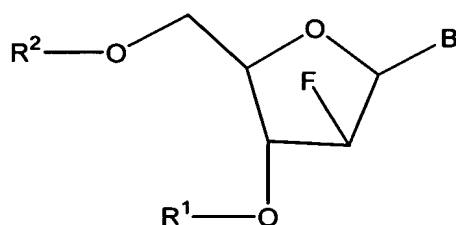
16. (Amended) The compound having the [general] formula:





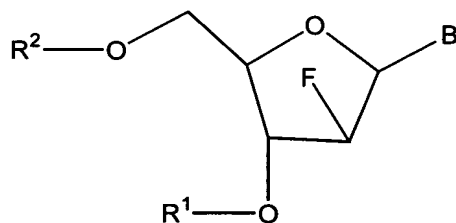
wherein B is N<sup>2</sup>-isobutyrylguanine, R<sup>1</sup> is t-butyldimethylsilyl and R<sup>2</sup> is H.

17. (Amended) The compound having the [general] formula:



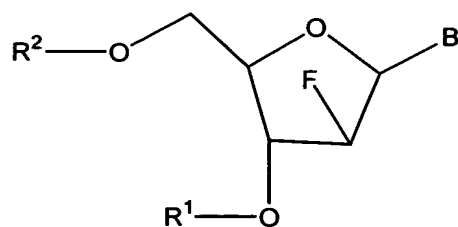
wherein B is N<sup>4</sup>-benzoylcytosine, R<sup>1</sup> is t-butyldimethylsilyl and R<sup>2</sup> is H.

18. (Amended) The compound having the [general] formula:



wherein B is N<sup>6</sup>-benzoyladenine, R<sup>1</sup> is t-butyldimethylsilyl and R<sup>2</sup> is H.

19. (Amended) The compound having the [general] formula:



wherein B is thymine, R<sup>1</sup> is t-butyldimethylsilyl and R<sup>2</sup> is H.